REMARKS

Claims 46-57 were pending in the present application. Claims 46 and 52 are amended; new claims 58-60 are added. Claims 46-60 are now pending. In the Office Action of 1 August 2002 the Examiner rejected Claims 46-49 and 51 under 35 U.S.C. §102(e) as having been anticipated by **Hofmann et al.** (U.S. Patent No. 5,817,630). The Examiner also rejected Claims 46, 48, and 49 under 35 U.S.C. §102(e) as having been anticipated by **Squires** (U.S. Patent No. 6,355,684). The Examiner also rejected Claims 52, 53 and 55 under 35 U.S.C. §102(b) as being anticipated by **Medow et al.** (U.S. Patent No. 3,943,251). In addition, the Examiner rejected Claim 50 under 35 U.S.C. §103(a) as being unpatentable over either **Hofmann et al.** of **Squires** in view of **Chiou** (U.S. Patent No. 5,182,258). The Examiner rejected Claims 47 and 51 under 35 U.S.C. §103(a) as being unpatentable over **Squires** in view of **Laub** (U.S. Patent no. 5,945,446). The Examiner rejected Claims 54 and 57 under 35 U.S.C. §103(a) as being unpatentable over **Medow et al.** in view of **Laub.** Finally, the Examiner rejected Claim 56 under 35 U.S.C. §103(a) as being unpatentable over **Medow et al.** in view of **Chiou.**

Rejections based on Hofmann et al.

Applicants respectfully traverse the anticipation rejections of Claims 46-49 and 51 based on **Hofmann et al.** This reference describes the use of lipoic acid as a therapeutic agent to increase the pliability of the ocular lens. The present application describes the use of naturally occurring compounds as microbicidal agents in ophthalmic solutions as preservatives and disinfectants. That is, while both **Hofmann et al.** and the current invention deal with the eye, they are directed at different applications. It is not correct to assume that all ophthalmic solutions are the same, with the same applications and uses. There are actually many different categories of ophthalmic solutions (e.g., therapeutics, artificial tears,

lubricants, antibiotics, anti-infective treatments, contact lens care products, etc.). Applicants believe that the use of the lipoic acid as a therapeutic does not anticipate the use of lipoic acid as a microbicidal compound in ophthalmic solutions.

Hofmann et al. describes eye drops, which use lipoic acid as an antioxidant. The present application describes the use of lipoic acid among other naturally occurring microbicidal compounds for use in hydrogen peroxide free ophthalmic solutions as preservatives and disinfectants. The **Hofmann et al.** eye drops are formulated to penetrate the cornea and treat the human lens. The function of the lipoic acid is to act as an antioxidant (column 1, lines 46-48). The reference describes the function of the antioxidants as scavenging free radicals and other oxidants, binding heavy metals, and preventing cross-linking of the collagen fibers (column 2, lines 57-59). There is no description for the use of lipoic acid as a preservative or disinfectant (microbicidal function as described in the present application). In fact **Hofmann et al.** indicates that because no preservative was used in the inventive eye drops, the eye drops must be refrigerated (see column 5, lines 27-28). Thus, **Hofmann et al.** does not recognize the use of the lipoic acid as an antimicrobial compound for ophthalmic solutions but rather uses lipoic acid as an anti-oxidant only.

Not only does **Hofmann et al.** not anticipate the use of lipoic acid as an antimicrobial agent, the reference also fails to render uses as a typical ophthalmic solution or as a contact lens solution obvious. One of the key performance attributes of an ophthalmic solution is the comfort of the solution during installation into the eye, especially for solutions intended to be used on a chronic basis (e.g., contact lens care solutions, artificial tears, etc.) **Hofmann et al.** indicates that use of the described eye drops results in burning sensation upon instillation (column 5, line 25). This might be acceptable in a therapeutic—in

Hofmann et al. the treatment is supposed to improve vision, However, the burning sensation would indicate that such eye drops are not useful for chronic use due to a lack of comfort—this would militate against common use as an ophthalmic ingredient. Further, **Hofmann et al.** describes the use of a penetrating agent, DMSO as being necessary for the inventive eye drops. As is known to those of ordinary skill in the art, DMSO is contra indicted for use with contact lenses due to the swelling effects of a solvent such as DMSO. Swelling damage and concentration of contact lens solution ingredients within the contact lenses is explained in the present specification. Since **Hofmann et al.** does not teach the use of lipoic acid apart from a penetrating agent such as DMSO, the **Hofmann et al.** reference cannot render a contact lens use of lipoic acid obvious.

The claims have been amended to remove lipoic acid from the general "ophthalmic solution". A new claim (Claim 58) has been added specifically directed to the microbicidal use of lipoic acid. Applicants submit that the new claim and the amended claims are now allowable and respectfully requests the Examiner to withdraw the rejections based on **Hofmann et al.**

Claim Rejections Based on Squires

Squires describes the use of a variety of botanical extracts—particularly Echinacea extract in combination with cationic surfactants—particularly benzalkonium chloride (BAK) as a treatment for herpes and other microbial infections. In the specification **Squires** mentions that this treatment could be useful in treating ocular tissue, conjunctiva and eyelids. No mention or claim is made for the use of the Echinacea extract alone, without the BAK or other cationic surfactant. The present application claims the use of Echinacea extract without the use of BAK or other disinfectant surfactants in ophthalmic solutions as a preservative or disinfectant. **Squires** indicates that Echinacea or BAK alone does

not perform as well as the combination (column 7, lines 24-30), and that the phytochemical agent must always be used in combination with an appropriate disinfecting surfactant (e.g. BAK). Thus, use of Echinacea alone as a microbicidal compound in ophthalmic solutions is not anticipated by **Squires**.

Further, Squires makes no mention of the use of Echinacea extract in combination with contact lenses or of the potential use of the Echinacea extract as a preservative in ophthalmic solutions. The preferred concentrations of Echinacea extract and BAK described by Squires would be contra-indicated for use with contact lenses and ophthalmic solutions due to the high tonicity (osmotic pressure) and high concentration of BAK (which has been shown to be toxic to ocular tissue whne used with soft contact lenses). Note that in many of the examples **Squires** describes a solution with 50 mg/ml of Echinacea. This translates to a concentration of 50,000 parts per million—well above the concentrations described in the present application. The range suggested by **Squires** (column 6, lines 17-23) is 2-90% (20,000 to 900,000 parts per million). whereas the range taught in the present application is 0.001% to 1.0% (10 to 10,000 parts per million). Since antimicrobial activity is generally directly related to concentration, the use of less concentrated solutions of the Echinacea extract is not obvious in light of **Squires**.

In addition, **Squires** describes the use of the treatment by cleaning and drying the tissue prior to application of the treatment to insure full activity of the treatment. This could not be accomplished with the current products used as ophthalmic solutions or in contact lens care. **Squires** indicates that the treatment needs to be in constant contact with the tissue, and that the patient should reapply the treatment as often as necessary to insure the coating is not diminished (column 6, lines 60 –63). This method cannot be rationally applied to ophthalmic solutions.

The claims have been amended so that Echinacea extract is claimed in a general ophthalmic solution only when the solution's preservative consists essentially of Echinacea in a range of concentrations below those of **Squires**. Further, Echinacea is separately claimed as a contact lens solution at concentrations below those suggested by **Squires**. Applicants respectfully contend that in view of the above discussion these claims are allowable and are not anticipated or rendered obvious by **Squires**.

Rejections based on Medow et al.

Medow et al. teaches that hydrasis compounds can be safely used in ophthalmic compositions as mild anesthetics and a agents to dilate the pupil of the eye. The reference teaches that the compounds will cause the pupils to remain dilated for up to about ten days. Further the reference teaches that the cornea is advantageously stained yellow-green by the material. Applicants have found that these materials are useful preservative/antimicrobial agents in contact lens solutions. Applicants believe that such a use is not anticipated by **Medow et al.** because inherent in a contact lens solution is the notion that the solution must not have unfavorable physiological or cosmetic effects. While slight numbing of the cornea might be considered an acceptable physiological effect, dilation of the pupil definitely is not an acceptable effect. Dilation can result in blurring of vision due to even minor refractory error as well as a significant danger of light damage to the retina. In addition, no one would sell, yet alone use, a contact lens solution that stained the eyes yellow-green. Although **Medow et al.** mentions that hydrastis compounds have favorable antimicrobial properties, one of ordinary skill in the art following that reference would not anticipate that concentrations of these compounds can be selected wherein the antimicrobial properties are preserved but the color and pupillary dilation properties are negligible. Applicants have found that it is possible to use these compounds to prevent microbial growth (i.e., act as a

preservative) in a contact lens solution without coloring the cornea or dilating the pupil. The claim has been amended to make this inherent feature of a contact lens solution explicit. Applicants respectfully request that the claim rejections based on **Medow et al.** be withdrawn.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner still finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (310) 734-5200 to discuss the steps necessary for placing the application in condition for allowance.

You are hereby authorized to charge any fees due and refund any surplus fees to our Deposit Account No. 50-1796.

Respectfully submitted,

CROSBY, HEAFEY, ROACH & MAY

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Red-lined Claim Copy (Revised Rule 121)

46. (Once Amended) A hydrogen peroxide-free ophthalmic solution comprised of between 10 and 10,000 parts per million of a naturally-occurring microbicidal compound selected from the group consisting of allicin, aucubin, bilberry extract, caffeic acid, chlorogenic acid, [echinacea extract,] ferulic acid, [lipoic acid,] naringin, oleuropein, proanthocyanidins, quercetin, and rutin.

52. (Once Amended) A contact lens solution containing a microbicidal concentration of [of] a naturally occurring microbicidal compound selected from the group consisting of berberine and hydrastine, wherein said microbicidal concentration does not color or dilate an eye in contact with said solution.

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